REMARKS

Clinically, recombinant human grown hormone (rhGH) is administered daily in growth hormone deficient patients. To decrease the dosing frequency and increase patient compliance sustained release formulations have been under development. These formulations have the potential to allow patients to decrease their dosing interval from daily to once or twice per month. The present invention addresses the release profile of sustained release formulations.

The present invention is drawn to a sustained release composition that uses a liquid carrier material (specifically, a non-polymeric, non-water soluble liquid material having a viscosity of at least 5,000 cP at 37°C that does not crystallize neat under ambient physiological conditions) to deliver multivalent metal cations and growth hormone. This composition provides a very low burst of from 0.1 to 2.2% in 24 hours, followed by protein release over 28 days. A comparative sustained release composition, identical except for substitution of sodium bicarbonate for multivalent metal cations, gives a much higher initial burst, 7-14% in 24 hours.

The rejection of claims 1, 2 and 26-30 under 35 U.S.C. § 102 over Jeng et al. is respectfully traversed. Claims 1, 2 and 26-30 of the present application are supported by provisional application 60/198,209 filed on April 19, 2000, and therefore Jeng et al. is not available as prior art against the present application. Furthermore, sucrose stearate and sucrose distearate are solids, not liquids, at both ambient and physiological temperatures.

The present application claims priority to provisional application 60/198,209 filed on April 19, 2000. The text and figures of this provisional application are the same as the present application as filed, except that the provisional application does not include the claims. On page 3, lines 13-15 of the provisional application, the disclosure of U.S. Patent No. 5,747,058 (Tipton et al.) is specifically incorporated by reference, and therefore applicant may look for support from this document in the determination of entitlement to the filing date of the provisional application.

Claims 1, 2 and 26 of the present application are supported by the provisional application. The broad description of the carrier material is supported by Tipton et al. at col. 2, lines 40-45. Growth hormone and the term "multivalent metal cation" are

supported by the provisional application, page 3, lines 16-20. The elements of the Markush group of claim 2 of the present application are supported by Tipton et al. at col. 6, lines 29-35 and col. 24, lines 14-15 (claim 84). Accordingly, claims 1, 2 and 26 of the present application are entitled to the priority date.

Claims 27-30 of the present application are also supported by the provisional application. Claim 27 is supported by the provisional application on page 6, lines 1-10 and Figure 2B. Claim 28 is supported by Figures 2B-C of the provisional application. Claims 29 and 30 are supported by the provisional application on page 6, line 5, and by the Figures. Accordingly, claims 27-30 of the present application are entitled to the priority date.

In the Office Action on page 5, the Office has taken the following position:

> In view of the similarity in structure, function, and utility between the sucrose distearate and sucrose stearate of Jeng et al. and Applicant's claimed liquid material, the former are deemed inherently to be non-water soluble, to have the same viscosity, and to not crystallize neat under ambient physiological conditions to the same extent claimed by Applicant.

Applicant respectfully disagrees with the Office's position. Sucrose distearate has a melting point of 60-68 °C and sucrose stearate has a melting point of 44-52 °C, as evidenced by the attached product description of CRODESTA SUGAR ESTERS, page 4, where the melting points of sucrose distearate (CRODESTA F-10) and sucrose stearate (CRODESTA F-160) are listed. Applicant submits Jeng et al. neither describes nor suggests a liquid carrier material, much less a liquid carrier material having a viscosity of at least 5000 cP at 37 °C.

Since claims 1, 2 and 26-30 are supported by the priority application, provisional application 60/198,209 filed on April 19, 2000, Jeng et al. with an earliest possible effective U.S. filing date of June 26, 2000, is not available as prior art against the present application. Furthermore, Jeng et al. neither describes nor suggests the use of a liquid carrier material as specified in the claims. Withdrawal of this ground of rejection is respectfully requested.

The rejection of the claims under 35 U.S.C. § 103 over European Patent Application 0 216 485 (EP '485) in view of Tipton et al. is respectfully traversed. EP '485 specifically uses an oil as an injectable liquid vehicle for the peptide growth

hormone. Extended release of the peptide growth hormone is achieved through the metal-complexed growth hormone either alone or in combination with optional solid extended release excipients or adjuvants. In contrast, Tipton et al. uses a liquid carrier material to provide for extended release of an active substance. Water soluble or miscible solvents are added to the composition containing the liquid carrier material merely to allow for administration, and the solvents quickly dissipate or diffuse away from the liquid carrier material upon administration, leaving a highly viscous liquid (the HVLCM) that provides desired extended release features for the composition.

EP '485 describes prolonged release of growth promoting hormones. This reference describes a formulation constructed by combining (admixing) an oil vehicle with an effective amount of a metal complex of a growth promoting hormone (page 2, lines 12-14, page 5, lines 13-21). The formulation my optionally further contain from 1-10% of known adjuvants or excipients (page 4, lines 6-17). The adjuvants and excipients are solids, and include beeswax, aluminum monostearate, camauba, and paraffin (page 4, lines 11-15). The formulations are administered via injection. Alternatively, the oil vehicle is not used, and the growth promoting hormone is administered using a mechanical implant containing a pump or matrix (page 5, lines 22-35).

The oil vehicle of EP '485 serves two purposes: first it is the liquid vehicle that allows for injection (page 4, lines 4-6), and secondly, the oil is used to restrict the growth hormone complex from any available body fluids upon administration (page 3, lines 32-35). Extended release is achieved by using metal complexes of the growth hormone, since they have a lower solubility than the free form of the hormone (page 2, lines 7-10); and enhanced extended release is achieved with the use of solid adjuvants or excipients (page 4, lines 11-13). When using an implant, which would physically prevent contact with body fluids upon administration, the metal complex and solid agents may be used, but the oil may be eliminated since its function is not needed (page 5, lines 31-35).

Tipton et al. describes high viscosity liquid controlled delivery systems. A composition for the controlled release of substances is formed by the combination of (i) a non-polymeric, non-water soluble high-viscosity liquid carrier material (HVLCM); and

(ii) a substance to be delivered (col. 2, lines 40-46). In one embodiment, the HVLCM is mixed with a water soluble or miscible solvent in order to form a lower viscosity mixture that is readily injectable (col. 2, lines 47-58). On administration, the solvent rapidly dissipates or diffuses away from the mixture, leaving *in-situ* a highly viscous implant or composition, i.e., the HVLCM and substance, which composition then releases the substance over time (col. 2, lines 59-63).

The composition containing the HVLCM significantly decreases in viscosity when mixed with a solvent to provide a composition that is typically easier to place in the body than just the HVLCM/substrate composition, because it flows more easily into and out of syringes or other implantation means, and can easily be formulated as an emulsion. In a preferred embodiment, the HVLCM is sucrose acetate isobutyrate (SAIB). SAIB is orally non-toxic and is used to stabilize emulsions in the food industry. It is a very viscous liquid and has an unusual property that there is a dramatic change in viscosity with small additions of heat or with the addition of solvents. It is soluble in a large number of biocompatible solvents. When in solution or in an emulsion, SAIB can be applied via injection or an aerosol spray. SAIB is compatible with cellulose esters and other polymers that can affect the rate of delivery of the substance. (Tipton et al., col. 5, line 50 to col. 6, line 28).

The high viscosity liquid carrier material of Tipton et al. does not provide the functions of the oil vehicle of EP '485, and therefore one of ordinary skill in the art would not substitute, e.g., the SAIB material of Tipton et al. for the oil vehicle of EP '485. The oil vehicle of EP '485 is used as the injectable liquid and also restricts the growth hormone complex from any available body fluids upon administration. The solvents of Tipton et al. are used to convert the HVLCM-containing composition to an injectable form, and dissipate or diffuse away upon administration. The extended release function in EP '485 is provided by the metal-complexed growth hormone, removing any reason for one of ordinary skill in the art to add the HVLCM (which provides the controlled release function of Tipton et al.) to the metal-complexed growth hormone. Accordingly, there would be no reason to make the substitution proposed in the Office Action, that is, to replace the oil vehicle of EP '485 with the HVLCM of Tipton et al. Applicant submits

that the claimed invention is not obvious over the applied references. Withdrawal of this ground of rejection is respectfully requested.

As further evidence of unobviousness, the claimed invention provides for an initial burst which is about ten times smaller than comparative compositions which do not contain multivalent metal cations, a much lower initial burst than would have been expected based on the teachings of EP '485. These unexpected and superior results demonstrate the unobviousness of the claimed invention.

EP '485 is described above. Example 5 is the only example which compares the release rates of compositions which are identical except for the presence of multivalent metal cations (pages 10-14). In this example, compound 1 contains peanut oil, 5% aluminum monosterate and 8 mg/ml of uncomplexed Parlow swine grown hormone; formulation 3 contains peanut oil, 5% aluminum monosterate and 8 mg/ml of zinc complexed growth hormone (page 10, lines 23-31). Tables 4 and 5 (pages 12 and 13) show the serum growth hormone levels for administration of the two compositions over a period of time. The earliest point in time after administration of the growth hormone for which both examples have data is at the 24 hour mark: serum growth hormone was 84.6 ng/ml for the uncomplexed growth hormone, and 40.0 ng/ml for the complexed growth hormone. This shows a decrease in the amount released of about 50% when multivalent metal cations are present. This is consistent with the 200% increase in release time of the growth hormone as concluded by this reference (page 14, lines 13-18).

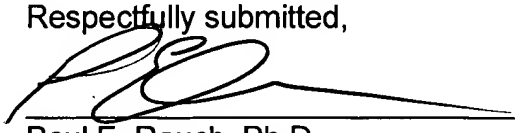
The claimed invention shows a greater than 10 fold drop in amount of growth hormone released within the first 24 hours, as compared to compositions without multivalent metal cations. Figure 4 includes release rate data for comparable compositions which either contain multivalent metal cations, or sodium bicarbonate (this experiment is described in the specification, page 6, lines 11-25). In the ethanol containing composition, 0.53% of the multivalent metal cation containing composition was released in 24 hours, while the otherwise identical sodium bicarbonate composition released 6.53% over 24 hours. In the benzyl benzoate containing composition, 1.06% of the multivalent metal cation containing composition was released within 24 hours, while the sodium bicarbonate composition released 14.64% over 24 hours. This data

indicates that the initial burst within 24 hours is reduced more than 10 fold when multivalent metal cations are present. Since EP '485 at best suggests a 2 fold decrease in initial burst within 24 hours, the present invention provides unexpected and superior results.

The comparison between the examples in the present application containing a multivalent metal cation (Zn^{2+}), and a monovalent metal cation (Na^{+}), is a closer comparison that any of examples of EP '485 would be, since more elements of the claims of the present application are met by the comparative examples of the present application than the examples of EP '485. The comparative examples of the present application meet all of the elements of the claims, except that the metal (Na^{+}) is monovalent instead of multivalent. In contrast, any comparison between the exemplified formulations of EP '485 and the claimed compositions of the present invention must consider entirely different kinds of pharmaceutical compositions that only have the metal complexed-growth hormone in common.. The data in the present application demonstrates the unobviousness of the claimed invention, since it provides a closer comparison than the examples of EP '485. Applicant submits that this provides further evidence of the unobviousness of the present invention.

Applicant submits that the present application is in condition for allowance. Early notice of such action is earnestly solicited.

Respectfully submitted,



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CRODESTA SUGAR ESTERS

Sucrose Fatty Acid Esters

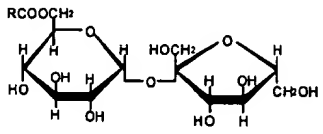
INCI Names:

CRODESTA F-10:	**Sucrose Distearate**
CRODESTA: F-110:	**Sucrose Stearate (and) Sucrose Distearate**
CRODESTA F-160:	**Sucrose Stearate**

CRODESTA F-10, CRODESTA: F-110, and **CRODESTA F-160** are esters of sucrose and fatty acids, and as a group, constitute a range of 100% active nonionic emulsifiers with various HLBs, allowing the formulation of both water-in-oil and oil-in-water emulsions. The **CRODESTAS** are mild, edible and ethylene oxide-free materials whose nonionic character makes them compatible with most cosmetic ingredients and synergistic with many other surfactants. As natural sugar esters, the **CRODESTAS** are classified as food grade emulsifiers (*CFR 21, Section* natural *172.859*), lending them use as emulsifiers and texturizers in foods, or as components in protective coatings for oral products.

The **CRODESTAS** are produced without ethoxylation, using a method that controls the degree of esterification (covered by U.S. Patent No. 3,480.616) and yields 100% active surface active agents, each with its own distinct HLB and structure, the latter of which may be monoester, diester or a combination thereof. (See structure below.)

Chemical Structure—Sucrose Monoester



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CRODA

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The individual ester composition of each **CRODESTA** determines the material as lipophilic or hydrophilic, as reflected in the value of its HLB. (See chart below.) For instance, sugar esters with a high monoester content tend to be hydrophilic and have high HLBs, lending them use in O/W emulsions; those with a high diester content are more lipophilic and have lower HLBs, making them suitable for W/O emulsions. Mono/diesters have properties and HLB values intermediate between the two.

CRODESTA	Ester Type	HLB
F-10	Diester	3.0
F-160	Monoester	14.5
F-110	Mono/Diester	12.0

The **CRODESTAS** display none of the drawbacks associated with ethoxylated ingredients, such as inverse solubility/temperature behavior or irritation potential. As emulsifiers, the **CRODESTAS** enable O/W systems to be formed at relatively low temperatures (45°C). In W/O systems, the two lower HLB **CRODESTAS** provide gelling action which helps stabilize the emulsion. Besides these applications, the **CRODESTAS** have use as wetting agents, dispersants, emollients and moisturizers. They leave a pleasant feel on the skin and are particularly desirable when mildness is an important factor. As such, they are recommended for products like facial or eye make-up, make-up removers, facial cleansers, and baby products.

CRODESTA F-10

CRODESTA F-10 is a diester with an HLB of 3. **CRODESTA F-10** produces W/O emulsions that form an emollient film that resists rinse-off. Such a film is desirable in baby products or sun-tanning lotions. Because this film acts as a plasticizer, **CRODESTA F-10** is also suitable for astringent-type products. Available as a creamy white powder, **CRODESTA F-10** is oil soluble (translucent) and water insoluble. Use level: 1-3%.

CRODESTA F-110

CRODESTA F-110 is a mixture of mono and diesters and has an HLB of 12.0. **CRODESTA F-110** is an especially mild O/W emulsifier and has been shown effective in reducing the irritation common to non-alkaline and non-soap containing emulsions. It is water soluble (translucent) and supplied in powdered form. Use level: 3-6%.

CRODESTA F-160

CRODESTA F-160 is a monoester with an HLB of 14.5 and functions as an O/W emulsifier. CRODESTA F-160 can be used as a wetting aid and foaming agent and displays interesting properties as a thickening and suspending agent in aqueous solutions. Its greatest value is in the production of microemulsions where its use as part of the surfactant blend tends to lower the irritation of these systems. CRODESTA F-160 is water soluble (translucent) and oil insoluble and is supplied as a white powder. Use level: 3-6%.

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APPLICATIONS

The **CRODESTAS** lend themselves to a variety of unique applications. Unlike many other hydrophilic surfactants, the **CRODESTAS** do not interfere with typical cosmetic active ingredients, nor interact with polyvalent salts and astringents. They also do not inactivate preservatives, anti-oxidants or other bio-active ingredients, making them excellent vehicles for delivering compounds of this type.

While the **CRODESTAS** confer unique properties to emulsions, to optimize their effects, it is recommended that certain adjustments be made during formulating. To achieve maximum stability in mixed phase systems, care should be taken to ensure optimal solubilization/dispersion. It is often better to blend a lower HLB surfactant with a higher one to effect this. As the higher HLB emulsifiers, **CRODESTAS F-110** and **F-160** can form jelly-like lumps on hydration, much like cellulose gum derivatives. This could prevent their complete solubilization, resulting in non-homogeneous mixtures. To avoid this, it is suggested that these particular **CRODESTAS** be either slurried into the oil phase at a fairly low temperature or incorporated into the water phase after being first dissolved in a glycol (i.e., propylene glycol, glycerin, PEG 200). This mixture can then be added to the oil phase.

Whether alone or in combination with other emulsifiers, the **CRODESTAS** can be used to produce elegant and eye-appealing skin care products. Such preparations leave a satiny smooth afterfeel on the skin. High HLB **CRODESTAS** create emulsions that form water-resistant films and have a strong affinity to skin. These emulsions have excellent spreading characteristics and can provide thixotropic or controlled pearling effects. As such, the **CRODESTAS** are excellent structural surfactants that can improve the spreadability, gloss and pigment dispersion of lipsticks, powders and water-in oil pigmented creams and lotions.

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Typical Analyses

	CRODESTA F-10	CRODESTA F-110	CRODESTA F-160
APPEARANCE	Powder	Powder	Powder
COLOR	White to Cream	White to Cream	White to Cream
ODOR	Faint, sweet	Faint, sweet	Faint, sweet
MELTING POINT	60-68°C	47-55°C	44-52°C
ACID VALUE	5.0 max.	5.0 max.	5.0 max.
SAPONIFICATION VALUE	140-200	85-145	80-140
HYDROXYL VALUE	80-130	440-490	500-550
IODINE VALUE	1.0 max.	1.0 max.	1.0 max.
MOISTURE CONTENT, %	2.0 max.	—	2.0 max.

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